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| 09/376,395 | 08/18/1999 | LEAF HUANG | 226272002201 | 6461 |

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MORRISON & FOERSTER LLP
755 PAGE MILL RD
PALO ALTO, CA 94304-1018

| EXAMINER |
|---|
| SCHNIZER, RICHARD A |

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Please find below and/or attached an Office communication concerning this application or proceeding.

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/376,395 | Huang |
| **Examiner** | **Art Unit** |
| Richard Schnizer | 1635 |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1) X Responsive to communication(s) filed on *Dec 9, 2002*.

2a) ☐ This action is **FINAL**. 2b) X This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

**Disposition of Claims**

4) X Claim(s) *77-86, 88-95, 97-101, 103-123, 125-131, and 133-155* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) X Claim(s) *77-80, 84-86, 88-95, 97-101, 103-110, 113-123, 125-131, and 133-1*[illegible] is/are rejected.

7) X Claim(s) *81-83, 111, and 112* is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9) ☐ The specification is objected to by the Examiner.

10) X The drawing(s) filed on *Aug 18, 1999* is/are a) ☐ accepted or b) X objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. §§ 119 and 120**

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) X Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1) X Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s).
4) ☐ Interview Summary (PTO-413) Paper No(s).
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

## DETAILED ACTION

An amendment was received and entered as Paper No 23 on 12/9/02.

In the previous Office Action the instant application was characterized as an RCE. This was incorrect. On 6/10/02 an acceptable request for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/376,395 was filed and a CPA was established. The current and previous Office Actions are in response to the CPA.

Claims 77-86, 88-95, 97-101, 103-123, 125-131, and 133-155 are pending and under consideration in this Office Action.

The invention as originally filed was drawn to drug compositions and methods of making and using them. In response to a restriction requirement, Applicant elected in Paper No. 10 group III drawn to therapeutic compositions comprising nucleic acids and methods of making and using them. Applicant also elected asialoglycoprotein as the species of targeting ligand to be examined. The species was deemed to read on all the claims. After a search of the prior art, it has been determined that claims 88 and 125 are novel and non-obvious with respect to the species of asialoglycoprotein. In accordance with MPEP 803.02, the Office has extended the search to a second species of targeting ligand, *i.e.* monoclonal antibodies, and has found prior art rendering obvious this species of claims 88 and 125. Claims 81-83, 111, 112, and 119-121 were found to be free of the art for all recited species.

***Priority***

1. The instant Application claims priority to two US Patents (5,795,587, filed 1,23/95; and 6,008,202, filed 9/29/97) and to abandoned application serial number 08/751,888, filed 11/18/96. Currently the application contains two claims (88 and 125), reciting compositions comprising an E1A gene. However, this embodiment finds no support in two of the three priority documents, US 5,795,587 and abandoned application serial number 08/939,874. For these reasons the effective filing date of claims 88 and 125 is 9/29/97. Similarly, support for shielding or PEG-modification of complexes is found only in US Patent 6,008,202, and not in the other two priority documents. So the priority date for claims 95, 97, 131, 133, 137, 138, 142, 143, 147-150, 154, and 155 is 9/29/97.

***Rejections Withdrawn***

2. The rejection of claims 77-86, 88-95, 97-101, 103-123, 125-131, and 133-155 under the judicially created doctrine of obviousness-type double patenting is withdrawn in view of Applicant's submission of a terminal disclaimer over US Patent 6,008,202. A new double patenting rejections is set forth below.

***Claim Objections***

3. Claims 81-83, 111, and 112 are objected to because they depend from a rejected claim, but would be allowable if rewritten in independent form with all of the limitations of the rejected base claim.

***Double Patenting***

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Claims 113-117, 126, 128-130, 134 and 135 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 7 of U.S. Patent No. 5,795,587 in view of Wu et al (J. Biol. Chem 263(29): 14621-14624, 1988) and Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992).

The claimed invention encompasses methods of delivering compositions to an individual. The compositions must comprise a nucleic acid, at least one lipid species, and a polycationic polypeptide salt. Claims 137-146, 154 and 155 require a targeting ligand. In Paper No. 10, Applicant elected asialoglycoprotein as the targeting ligand under consideration. Claims 113-120, and 122-155 allow the complex to have a positive, neutral, or negative charge. Claims 113-123, 125-131, 133-136, and 147-153 recite various routes of administration including systemic (intravenous).

Claim 6 of '587 teaches nucleic acid/lipid/polycationic polypeptide complex with a net positive charge, wherein the lipids include DC-Chol and a neutral colipid, and the polypeptide is polylysine with a molecular weight of between 300-200,000. This molecular weight range overlaps the range of polypeptide lengths recited in instant claim 128. Claim 7 of '587 requires that the size of the particles must be less than 400 nm. Claims 9-11 of '587 recite rations of lipids, nucleic acids, and polycations, overlapping those required by instant claim 134.

Claims 6 and 7 of '587 do not require deliver of the complexes to an individual.

Mack teaches that addition of a cationic lipid (DOGS) to asialoglycoprotein-modified polylysine/gene complexes improves transfection efficiency.

Wu teaches a method of intravenously delivering to cells of an individual *in vivo* DNA encoding a reporter gene (chloramphenicol acetyltransferase). Wu teaches the formation of complexes between the DNA and asialoglycoprotein-modified polylysine. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to deliver the complexes of '587 in vivo, because Mack teaches complexes having all of the characteristics of claims 113-117, 126, 128-130, 134 and 135, and Wu teaches that asiaologlycoprotein-targeted nucleic acid particles should be delivered in vivo. In view of the results of Wu, one would have a reasonable expectation of success for in vivo delivery of these particles.

6. Claims 122, 123, and 127 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 6 of U.S. Patent No. 5,795,587, Wu et al (J. Biol. Chem 263(29): 14621-14624, 1988) and Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992) as applied to claims 113-117, 126, 128-130, 134 and 135 above, and further in view of Birnstiel et al (US Patent 5,922,859, issued 7/13/99).

Mack teaches methods of preparing complexes of asialoglycoprotein-modified polylysine, plasmid DNA, and cationic lipids.

Wu teaches that particles similar to those of Mack, but lacking lipids, can be used to successfully delivery of DNA to an individual in vivo. Mack teaches that addition of cationic lipids increases transfection efficiency.

These references do not teach a polycationic polypeptide comprising at least 30% arginine residues and less than 5% lysine residues, nor do they teach a sulfate salt, protamine as a polycation.

Birnstiel teaches methods and compositions for delivering DNA to cells. The complexes comprise a polycationic polypeptide salt for condensing the DNA, as well as a targeting ligand. See e.g. claims 1, 14, and 17. Birnstiel also teaches that protamine sulfate and polylysine may be used interchangeably in such compositions. See column 18 line 66 to column 19, line 25. The polylysine may be 55 or 90 amino acids in length. See column 18, lines 5-11. Alternatively, the polycation may be an arginine-rich polypeptide of 36 amino acids comprising 13 arginines (36%), and 1 lysine (2.7%) (see column 19, lines 28-38).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polycations of Birnstiel in the methods and compositions of Wu and Mack or '587. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Also, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, the polycationic polypeptide salts of Birnstiel are clearly equivalent to the polycations of Wu

and Mack because all of these polycations function to condense DNA for cellular delivery, and also serve as a carrier for a targeting ligand.

Thus the invention as a whole was prima facie obvious.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 113-123, 125-131, and 133-153 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of delivering in vitro or systemically in vivo a composition comprising at least one lipid species, a polycationic polypeptide salt, and a reporter gene, and for methods of delivering directly to the site of a tumor a composition comprising at least one lipid species, a polycationic polypeptide salt, and an E1A gene, as taught in US Patent 6,008,202, wherein the composition has a net positive charge, does not reasonably provide enablement for methods of delivering therapeutic genes systemically, or for methods of delivering the E1A in gene in compositions comprising a net neutral or negative charge. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with the claims.

*Nature of the invention and Breadth of the claims*

8. The claimed invention encompasses methods of delivering compositions to an individual. The compositions must comprise a nucleic acid, at least one lipid species, and a polycationic polypeptide salt. Claims 137-146, 154 and 155 require a targeting ligand. In Paper No. 10, Applicant elected asialoglycoprotein as the targeting ligand under consideration. Claims 113-120, and 122-155 allow the complex to have a positive, neutral, or negative charge. Claims 113-123, 125-131, 133-136, and 147-153 recite various routes of administration including systemic (intravenous).

The specification teaches two apparent purposes for delivering a nucleic acid to an individual in vivo, for therapy or diagnostic effect. In order to enable the full scope of the claims and elected invention requires that the nucleic acid is intended to be used as a drug. It is clear that one can use the claimed invention to deliver reporter constructs and to achieve detectable expression of reporter genes. However, in order to enable the invention commensurate in scope with the claims, the specification must also teach how to use the claimed compositions therapeutically.

*State of the art, Predictability of the art, and Level of skill of those in the art*

9. At the time the invention was made, successful implementation of gene therapy protocols was not routinely obtainable by those skilled in the art. This is reflected by three recently published reviews. Orkin (Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy, 1995) teaches that "significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all

current transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host" (page 1, item 3). Orkin teaches that problems exist in delivering nucleic acid sequences to the appropriate target cell or tissue and achieving the appropriate level of expression within that cell or tissue (page 9). Verma et al (Nature 389: 239-242, 1997) teach that "there is still no single outcome that we can point to as a success story (p. 239, col 1). The authors state further, "Thus far, the problem has been the inability to deliver genes efficiently and to obtain sustained expression" (p.239, col. 3). Anderson (Nature 392:25-30, 1998) confirms the unpredictable state of the art, stating that "there is still no conclusive evidence that a gene-therapy protocol has been successful in the treatment of human disease" (p. 25, col. 1) and concluding, "Several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered" (p.30). Because the existing delivery and expression techniques cannot be used to predictably treat diseases, it is necessary for the specification to provide guidance to the skilled artisan as to how to overcome the factors which hamper gene delivery and expression such that a therapeutic result is achieved. It is noted that because the claims encompass gene therapy generally, the scope which must be enabled is very broad and includes the treatment of any disease with any gene.

Consideration of Example 18 also raises the issues of systemic versus local delivery, and the use of targeting ligands. This example employs direct injection at the site of the tumor, whereas the claims encompass systemic intravenous delivery. While progress has been made in recent years for *in vivo* gene transfer, vector targeting *in vivo* to desired organs continues to be

unpredictable and inefficient. This is supported by numerous teachings available in the art. For example, Miller et al. reviews the types of vectors available for *in vivo* gene therapy, including retroviral, adenoviral, liposomal, and molecular conjugates, and conclude that "for the long-term success as well as the widespread applicability of human gene therapy, there will have to be advances...targeting strategies outlined in this review, which are currently only at the experimental level, will have to be translated into components of safe and highly efficient delivery systems" (page 198, column 1). Deonarain (1998) reviews ligand-targeted receptor mediated vectors, and indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Deonarain reviews new techniques under experimentation in the art which show promise, but which are currently even less efficient than viral gene delivery (see page 65, first paragraph under Conclusion section). Verma et al. (1997) reviews various vectors known in the art for use in gene therapy and the problems which are associated with each. Verma clearly indicates that at the time of the claimed invention resolution to vector targeting had not been achieved in the art (see entire article). Crystal also reviews various vectors known in the art and indicates that "among the design hurdles for all vectors are the need to increase the efficiency of gene transfer, to increase target specificity and to enable the transferred gene to be regulated" (page 409). Thus the general state of the art for targeted delivery of nucleic acids is immature in the context of therapeutic applications, necessitating direct administration of nucleic acids to the intended target site, rather than systemic administration. In

summary, those of skill in the art of gene therapy at the time of the invention considered the field to be extremely difficult and unpredictable, such that even those of the highest level of skill could not routinely practice gene therapy with success.

*Guidance and Working examples in the specification*

10. The specification teaches a working example of gene therapy in which the survival of mice injected intraperitoneally with tumor cells is prolonged by subsequent intraperitoneal administration of compositions comprising cationic polypeptides, lipids, and a nucleic acid encoding an E1A polypeptide. The specification fails to disclose the net charge of these compositions. See example 18, pages 53 and 54. US Patent 6,008,202, issued to Applicant, discloses the identical working example, and recites claims drawn to drug/lipid/polycationic polypeptide compositions comprising a net positive charge. See claim 2 of '202'. This patent is presumed to be valid, thus compositions comprising the net positive charge are presumed to be enabled. However, as one of skill in the art appreciates that most cells carry a net negative surface charge, delivery compositions of net negative or neutral charge would reasonably be expected to interact differently with target cells than would compositions of net positive charge. Such compositions are embraced by all claims except claims 116, 117, 120, and 121. Clearly, the interaction of the composition with target cells is of critical importance to the function of the invention. In the absence of a targeting ligand, one of skill in the art would reasonably expect that the affinity of the net neutral or negative compositions for a given cell would be less than that of a positively charged composition. Because the specification does not disclose a working example of

the compositions in gene therapy, and due to the unpredictability associated with the delivery of gene therapeutics as set forth by Orkin, Verma, and Anderson above, it is not clear that negative or neutral compositions would provide the same benefit as the positively charged versions. Furthermore, the claims broadly encompass compositions and methods for the purpose of gene therapy in general. This scope encompasses the treatment of any disease, and with the exception of claim 125 which recites the E1A gene, any gene may be used for treatment. However, the E1A gene is the only example of a therapeutic gene disclosed in the specification, and the specification. teaches how to treat only one disease with this gene.

*Amount of experimentation required to practice the invention*

11. In view of the broad scope encompassed by the claims, The state and unpredictability of the art of gene therapy in general, the disclosure of only a single positively charged therapeutic gene complex useful to treat only one disease, and the lack of guidance with regard to systemic therapeutic gene delivery, one of skill in the art would have to perform undue experimentation in order to practice the invention commensurate in scope with the claims.

***Response to Arguments***

Applicant's response filed 12/9/02 has been fully considered but is not persuasive.

12. The portion of the previous rejection concerning the asialoglycoprotein targeting factor has been withdrawn in view of Applicant's arguments and the art rejections below. Applicant's arguments with regard to the enablement of diagnostic embodiments is persuasive, and the

rejection has been modified to reflect this. With respect to the "gene therapy" aspects of the rejection, Applicant argues at page 3, paragraph 2 of the response that the claimed complex is not intended to be a drug. However, Applicant admits that the complex may be used to carry either a therapeutic or a diagnostic agent. It follows that claims to delivery of the complex in vivo must be considered in light of both therapeutic and diagnostic applications. Applicant has not responded to the rejection in terms of how the specification enables the broad aspects of gene therapy, i.e. delivery of any therapeutic gene by any route. For this reason the rejection is maintained.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

13. Claims 77-79, 89, 93, 94, 98-100, 104, 107-109, 139-141, and 144-146 are rejected under 35 U.S.C. 102(b) as being anticipated by Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992).

Mack teaches methods of preparing complexes of asialoglycoprotein-modified polylysine, plasmid DNA, and cationic lipids, and methods of using the complexes to transfect liver cells (see abstract). The complexes have a net positive charge (see page 139, column 2, third full

paragraph. Absent evidence to the contrary, the positive charge is on the surface of the particles, as required by claim 79. Association of positively charged polylysine/DNA complexes with cationic lipids should reasonably result in binding of the hydrophobic portion of the lipids with the hydrophobic portions of the polylysine/DNA complex, and sequestration of these portions away from the hydrophilic medium, resulting in a positively charged surface. The ratio of nucleic acid:lipid:polycation is 1 microgram : 103 nmol : 3 microgram, assuming a molecular weight of 807 D for the cationic lipid DOGS, and use of 8.3 micrograms of DOGS. See Fig. 2 on page 140. This ratio is in the range of ratios required by claims 93 and 99. The mean diameter size of the complexes ranges from about 280 to 560 nanometers (see Fig. 4 on page 140), meeting the limitations of claim 94.

Thus Mack anticipates the claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

14. Claims 80, 84-86, 91, and 103 are rejected under 35 U.S.C. 103(a) as being unpatentable over Birnstiel et al (US Patent 5,922,859, issued 7/13/99) in view of Mack et al (Am. J. Med. Sci. 307(2): 138-143, 1992).

Birnstiel teaches methods and compositions for delivering DNA to cells. The complexes comprise a polycationic polypeptide salt for condensing the DNA, as well as a targeting ligand. See e.g. claims 1, 14, and 17. Birnstiel also teaches that protamine sulfate and polylysine may be used interchangeably in such compositions. See column 18 line 66 to column 19, line 25. The polylysine may be 55 or 90 amino acids in length. Alternatively, the polycation may be an arginine-rich polypeptide of 36 amino acids comprising 13 arginines (36%), and 1 lysine (2.7%) (see column 19, lines 28-38.

Birnstiel does not teach the addition of lipids to these complexes.

Mack teaches complexes of targeted polycationic polypeptide salts and DNA to which cationic lipids are added.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Birnstiel by addition of cationic lipids as taught by Mack. One would have been motivated to do so because Mack teaches that addition of cationic lipids to targeted polycationic polypeptide salt/nucleic acid complexes increases transfection efficiency.

Thus the invention as a whole was prima facie obvious.

15. Claims 88 and 125 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hung et al (US Patent 5,651,964, issued 7/29/97), in view of Trubetskoy et al (1992), Mack (1992), and Kern et al (CANCER RESEARCH, (1990 Aug 15) 50 (16) 5184-7).

Hung teaches methods of suppressing growth of a neu-oncogene-mediated tumor in a mammal by delivery to the tumor of a plasmid comprising a nucleic acid sequence encoding an adenoviral E1A gene product. See claim 2.

Hung does not teach a composition comprising a polycationic polypeptide salt, a nucleic acid, a lipid, or a targeting moiety.

Trubetskoy teaches of antibody-modified polylysine, plasmid DNA, and cationic liposomes, and methods of using the complexes to transfect mouse lung endothelial cells (see abstract).

Mack teaches that addition of cationic lipids to targeted polylysine/gene complexes improves transfection efficiency above that obtained in the absence of lipids and/or polycations. See Fig 2 at page 140.

Kern teaches that neu is overexpressed in several types of lung cancer. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the invention of Hung by complexing the E1A-encoding plasmid with the targeted polycationic polypeptide and liposomes of Trubetskoy for delivery to mouse lung cells in vivo. One would have been motivated to do so because Mack teaches that addition of targeted polycations and cationic lipids to plasmid DNA improves transfection efficiency. One would have

been motivated to deliver the complexes to a lung tumor because Kern teaches that many lung tumors are characterized by overexpression of neu. One would have had a reasonable expectation of success because the targeting ligand of Trubetskoy mediated successful transfection of mouse lung cells in vitro.

16. Claims 105, 113-117, 126, 130, 134-136, and 151-153 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu et al (J. Biol. Chem 263(29): 14621-14624, 1988) in view of Mack et al (1992).

Wu teaches a method of intravenously delivering to cells *in vivo* DNA encoding a reporter gene (chloramphenicol acetyltransferase). Wu teaches the formation of complexes between the DNA and asialoglycoprotein-modified polylysine. See abstract.

Wu does not teach the addition of lipids to the complex.

Mack teaches that addition of a cationic lipid (DOGS) to asialoglycoprotein-modified polylysine/gene complexes improves transfection efficiency. See abstract and page 138, column 2, lines 1-4 and 18-22.

It would have been obvious to one of ordinary skill in the art at the time of the invention to add DOGS to the complexes of Wu because Mack teaches that addition of DOGS improves transfection efficiency.

Thus the invention as a whole was prima facie obvious.

17. Claims 90, 92, 101, 106, 127, 129 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu and Mack as applied to claims 105, 113-117, 126, 130, 134-136, and 151-153 above and further in view of Trubetskoy et al (1992), and Harris et al (US Patent 5,650,096, issued 7/22/97).

Wu and Mack can be combined to render obvious methods of delivering to cells in vivo nucleic acids encoding a reporter gene by contacting the cells with complexes comprising a targeting ligand-modified polycationic polypeptide salt, the nucleic acid, and the cationic lipid DOGS.

These references do not teach compositions comprising the cationic lipid DC-Chol, or a neutral colipid.

Trubetskoy teaches methods of preparing complexes of a targeting antibody-modified polycationic polypeptide salt, plasmid DNA, the cationic lipid DC-Chol and the neutral lipid DOPE. See Abstract and paragraph bridging pages 311 and 312.

Harris teaches that the cationic lipids DC-Chol and DOGS are both cationic amphiphiles useful for the delivery of nucleic acids. See column 4, lines 19-29. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Also, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use

supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, the utility of DC-Chol, and DOGS, in DNA delivery complexes was well known in the prior art, so it would have been obvious to substitute DC-Chol for DOGS. It would have been further obvious to include a neutral colipid as taught by Trubetskoy, particularly because it was well known in the art that neutral colipids should be included with cationic lipids to facilitate delivery to cells of DNA. See e.g. Harris column 3, lines 14-19.

Thus the invention as a whole was prima facie obvious.

18. Claims 118, 122, 123, and 128 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu and Mack as applied to claims 105, 113-117, 126, 130, 134-136, and 151-153, and further in view of Birnstiel et al (US Patent 5,922,859, issued 7/13/99) .

Wu and Mack can be combined to render obvious methods of delivering to cells in vivo nucleic acids encoding a reporter gene by contacting the cells with complexes comprising a targeting ligand-modified polycationic polypeptide salt (asialoglycoprotein-modified polylysine), the nucleic acid, and a cationic lipid.

These references do not teach a polycationic polypeptide comprising at least 30% arginine residues and less than 5% lysine residues, nor do they teach a sulfate salt, protamine as a polycation, or a polycationic polypeptide of 20-100 amino acids in length.

Birnstiel teaches methods and compositions for delivering DNA to cells. The complexes comprise a polycationic polypeptide salt for condensing the DNA, as well as a targeting ligand. See e.g. claims 1, 14, and 17. Birnstiel also teaches that protamine sulfate and polylysine may be used interchangeably in such compositions. See column 18 line 66 to column 19, line 25. The polylysine may be 55 or 90 amino acids in length. See column 18, lines 5-11. Alternatively, the polycation may be an arginine-rich polypeptide of 36 amino acids comprising 13 arginines (36%), and 1 lysine (2.7%) (see column 19, lines 28-38).

It would have been obvious to one of ordinary skill in the art at the time of the invention to use the polycations of Birnstiel in the methods and compositions of Wu and Mack. MPEP 2144.06 indicates that it is obvious to substitute for one another components that are known in the prior art to have equivalent characteristics in the claimed environment. Furthermore, an express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Also, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case, the polycationic polypeptide salts of Birnstiel are clearly equivalent to the polycations of Wu and Mack because all of these polycations function to condense DNA for cellular delivery, and also serve as a carrier for a targeting ligand.

Thus the invention as a whole was prima facie obvious.

19. Claims 95, 97, 131, 133, 137, 138, 142, 143, 147-150, 154, and 155 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wu and Mack as applied to claims 105, 113-117, 126, 130, 134-136, and 151-153, and further in view of Torchilin et al (FASEB J. 6(9): 2716-2719, 1992)

Wu and Mack can b combined to render obvious a method of intravenously delivering to cells DNA encoding a reporter gene (chloramphenicol acetyltransferase), wherein the DNA is complexes with a ligand-modified polycationic polypeptide and a lipid. These references do not teach shielding of the complex, or modification with polyethylene glycol (PEG).

Torchilin teaches that PEG-modification of targeted liposomes is advantageous for intravenous delivery because it allows prolonged circulation and avoidance of rapid clearance. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to shield the composition of Wu and Mack by attachment of polyethylene glycol. One would have been motivated to do so because Torchilin teaches that this overcomes the problem of rapid particle clearance from the bloodstream, thereby increasing the chance of accurate targeting.

Thus the invention as a whole was prima facie obvious.

***Summary***

Claims 81-83, 111, and 112 are objected to because they depend from a rejected claim, but would be allowable if rewritten in independent form with all of the limitations of the rejected base claim.

Claims 113-123, 125-131, and 133-153 are rejected under 35 U.S.C. 112, first paragraph.

Claims 77-79, 89, 93, 94, 98-100, 104, 107-109, 139-141, and 144-146 are rejected under 35 U.S.C. 102(b).

Claims 80, 84-86, 88-92, 95, 97, 101, 103, 15, 106, 113-118, 122, 123, 125-131, 134-138, 142, 143, and 147-15 are rejected under 35 U.S.C. 103(a).

***Conclusion***

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JEFFREY SIEW
PRIMARY EXAMINER
2/24/03